Overview of Renal Function

- The kidneys are both excretory and regulatory organs. By excreting water and solutes, the kidneys rid the body of excess water and waste products.
- They also regulate the volume and composition of the body fluids within a very narrow range, despite wide variations in the intake of food and water.
- Because of the kidney's homeostatic functions, the tissues and cells of the body are able to carry out their normal functions in a relatively constant environment.
- Thus, the kidneys have several major regulatory functions, which include:

1. Regulation of water and electrolyte balance:

For regulation of homeostasis, excretion of water and electrolytes must be precisely matched to intake.

2. Excretion of metabolic waste products:

The kidneys are the primary means for eliminating waste products of metabolism. These products include urea, uric acid, creatinine, metabolites of various hormones and bilirubin.

3. Excretion of foreign chemicals, e.g. drugs, food additives and pesticides.

4. Regulation of arterial blood pressure:

I. Short-term regulation: renin-angiotensin aldosterone system.

II. Long-term regulation: through excreting variable amounts of sodium and water.

5. Regulation of acid-base balance by:

a) Elimination of acids produced from the metabolism of proteins such as sulphuric and phosphoric acid.

b) Regulation of the buffer stores in the body.

6. Gluconeogenesis:

The kidneys synthesize glucose from amino acids during prolonged fasting and add it to the blood. This helps to maintain blood glucose concentration.

7. Secretion of prostaglandins (PGE2, PGI2) and bradykinins.

These act as paracrine hormones that play important role in regulation of the renal blood flow.

8- Endocrine functions of the kidney:

a) Regulation of erythrocyte production:

- The kidneys secrete erythropoietin (EPO) hormone, which stimulates the production of R.B.Cs. The kidneys account for almost all the erythropoietin secreted into the circulation. Severe anaemia develops in people with severe kidney disease as a result of decreased erythropoietin production.

- The introduction of recombinant human EPO greatly benefited patients with chronic kidney disease (CKD) by improving their debilitating symptoms, and freeing them from dependence on blood transfusions.

b) Regulation of 1,25-Dihydroxy vit. D_3 production:

- The kidneys produce the active form of vitamin D: 1,25-dihydroxycholecalciferol by hydroxylating this vitamin at the number "1" position. Active vitamin D plays an important role in calcium and phosphate homeostasis.

- Chronic renal failure can lead to weak bone .

N.B: **Renal osteodystrophy causes:**

1- Decreased activation of vitamin D with impaired

intestinal absorption of calcium.

2- Retention of phosphate by diseased kidneys disturbs the calcium level

3-Secondary hyperthyroidism to correct the calcium level

a) *Renin secretion.*

- It is formed by juxtaglomerular apparatus which controls the formation of angiotensin II. This helps in normal regulation of arterial blood pressure and sodium balance.
- In conditions with impaired local blood flow to kidney due to narrow vasculature with atherosclerosis , bilateral renal stenosis or in diabetes mellitus the kidneys behave as if there is systemic hypotension trying to correct it by increasing renin angiotensin formation so hypertension occur. Therefore inhibition of angiotensin II formation or blocking its receptors is considered the main line of treatment of hypertension in this condition.

N.B: Inhibition of angiotensin II formation (ACE inhibitors) or blocking its receptors (ARBs) is found to delay the progression of diabetic nephropathy and proteinuria.

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111Equation Chapter 1 Section 1Formation of Urine

Each nephron is capable of forming urine by three processes:

1) Glomerular filtration:

Filtration from the glomerular capillaries into Bowman's capsule of a fluid that is nearly free of proteins.

2) Tubular reabsorption:

It is the transfere of water and solutes from the filtrate back into the blood of the peritubular capillaries.

3) Tubular secretion:

It is the transfer of solutes from the peritubular capillaries into the tubular lumen.

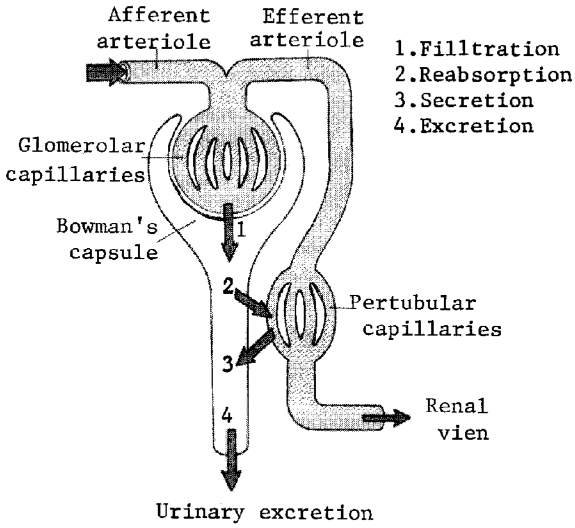
- The term excretion refers to what finally comes out in urine.
- The rate at which different substances are excreted in urine represents the sum of the three processes.

Urinary excretion rate =

Filtration rate - reabsorption rate + secretion rate.

Fig. (2-1), shows the basic mechanisms of nephron function.

Fig. (2-



Glomerular Filtration

20 % Of the plasma flowing through the kidneys is filtered by the glomerular capillaries into Bowman’s capsule. The filtered fluid is called Glomerular filtrate.

Composition of the Glomerular filtrate:-

Fluid filtered by the glomerulus is protein-free ultrafiltrate of plasma i.e. plasma minus colloids.

Glomerular membrane: -

The membrane that separates the blood in the glomerular capillaries from the Glomerular filtrate in Bowman’s capsule is formed of three layers. (Figs.2-2 & 2-3).

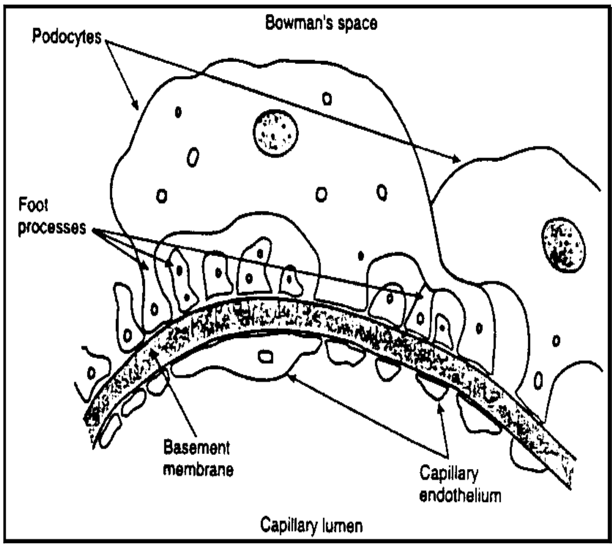


Fig. (2-2)

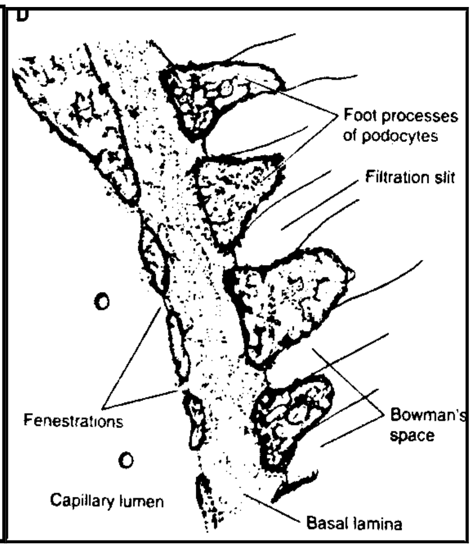


Fig. (2-3)

1. *The capillary endothelium'*. It is perforated by small holes called fenestrae.

   This layer does not act as a major barrier for plasma proteins as the fenestrations are relatively large (70-90 nm in diameter).

2. *Basement membrane:* It consists of a meshwork of collagen and proteoglycan fibrillae that have large spaces. The proteoglycan carry strong negative electrical charges, therefore, the basement membrane prevents effectively filtration of plasma proteins, but filters large amounts of water and solutes.

3. *Podocytes:* These are epithelial cells that line the outer surface of the glomerulus. They have numerous pseudopodia that interdigitate to form slit pores (25 nm wide) through which the glomerular filtrate moves.

Mesangial cells: These are stellate cells located between the basement membrane and the endothelium at bifurcation of the capillaries (Fig. 2-4). These cells are contractile.

Function of the mesangial cells:

Play role in regulation of glomerular filtration rate as their contraction will reduce the surface area available for filtration on the

other hand their relaxation increases surface area.

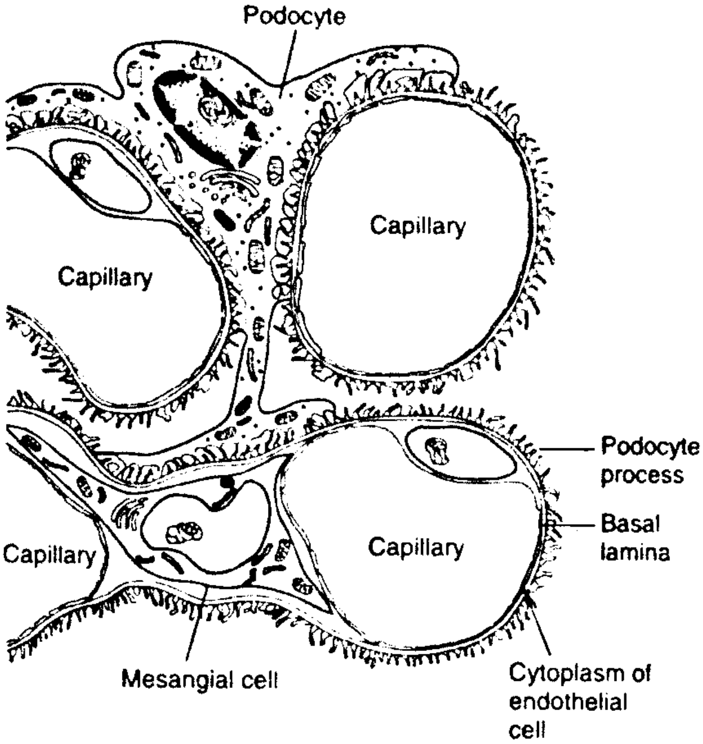


Fig. (2-4) Relations of mesangial cells & podocytes to glomerular capillaries

- ## Surface area of the glomerular membrane:

The total surface area of the glomerular membrane across which filtration occurs in humans is about 0.8 m^2.

- ## Permeability of the glomerular membrane:

The permeability of the glomerular capillaries is about 50 times that of the capillaries in skeletal muscle.

Despite the tremendous permeability of the glomerular membrane, it is highly selective in determining which molecules will filter. This high selectivity is determined by:

1) Size of the solutes.

2) Electric change of the solute.

1) Size of the solute:

The permeability of the glomerular membrane to solutes decreases with increasing the molecular diameter. Neutral substances with effective molecular diameter of less than 4 nm are freely filtered and the filtration of neutral substances with diameter of more than 8 nm approaches zero.

Between these values, filtration is inversely proportionate to diameter (Fig. 2-5).

2) Charge of the solutes:

Negatively charged molecules are filtered less easily than positively charged molecules of equal molecular diameter due to the negative charges in the basement membrane (Fig. 2-5)

This may explain why albumin with effective molecular diameter of approximately 7 nm, has a glomerular concentration only 0.2% of its plasma concentration than the higher concentration that would be expected on the basis of diameter alone (Circulating albumin is negatively charged).

In certain kidney diseases, the negative charges on the basement membrane are lost leading to loss of albumin in urine (Albuminurea) without an increase in the size of the pores in the membrane.

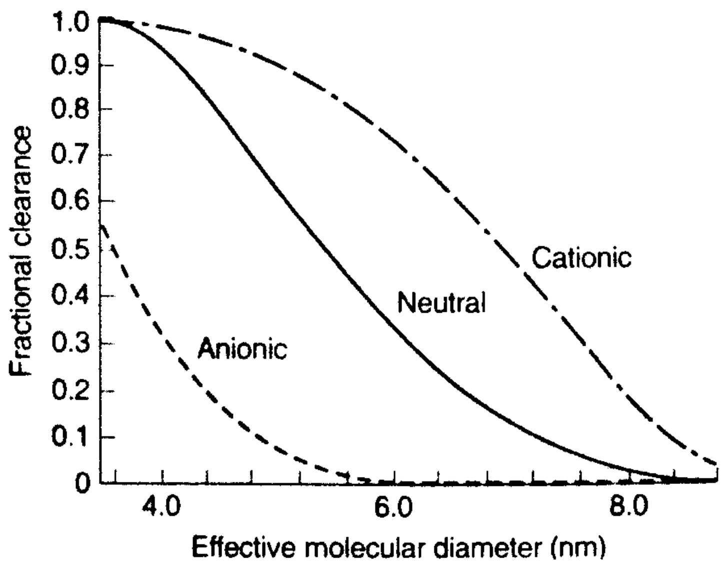


Fig. (2-5)

Glomerular Filtration Rate (GFR):

* *Definition:* Volume of the glomerular filtrate formed by the glomeruli of both kidneys per minute.

- **Normal GFR:**

- The GFR in an average - sized normal man is approximately 125 ml/min.

Values in women are 10% less than those in men.

- It should be noted that 125 ml/min is 7.5 L/h or 180 L/day whereas normal urine volume is about 1 L /day.

Therefore 99% or more of the filtrate is reabsorbed by the renal tubule.

At the rate of 125 ml/min, the kidneys filter in one day an amount of fluid equal to 60 times the plasma volume.

- Both BUN and plasma creatinine increase when GFR decreases.
- GFR decreases by 1ml/min/year after age 40 as part of aging process , although plasma creatinine remains constant because of decreased muscle mass.
- GFR is considered the best test for kidney functions.

Filtration fraction:

Is the fraction of renal plasma flow filtered across the glomerular capillaries, i.e. the ratio of GFR to the renal plasma flow.

Normal value 0.16 - 0.20.

Thus, about 20% of the RPF is filtered. The remaining 80% leaves the glomerular capillaries by the efferent arterioles and became the peritubular capillary circulation.

Control of GFR:

The factors govering filtration across the glomerular capillaries

are the same as those govering filtration across all other capillaries.

These factors include:

1. Hydrostatic pressure gradient across capillary wall.
2. Osmotic pressure gradient across capillary wall.
3. Permeability of the glomerular capillaries.
4. Effective filtration surface area.

These factors are summarized by the Starling equation:

The GFR = K_F (HP_Gc - HP_{BC}) - (πGC - π_{BC})

= K_F (HP_{GC} - HP_{BC} - π_{GC} + π_{BC})

Where:

K_F = The glomerular ultrafiltration co-efficient (ml/min/ mrnHg)

HP_{GC} = The mean hydrostatic pressure in the glomerular capillaries (mmHg).

HP_{BC} = The mean hydrostatic pressure in Bowman's capsule (mmHg).

π_{GC} = The osmotic pressure of plasma proteins in the glomerular capillaries (mmHg).

π_{BC} = The osmotic pressure of proteins in the filtrate (mmHg).

Forces favouring filtration (mmHg):

1- **HP_{GC}**: approximately 60 mmHg.

2- **π_{BC} :** normally 0 mmHg because almost no protein is filtered across the glomerular capillaries. They are repelled by the negative charges on the glomerular membrane.

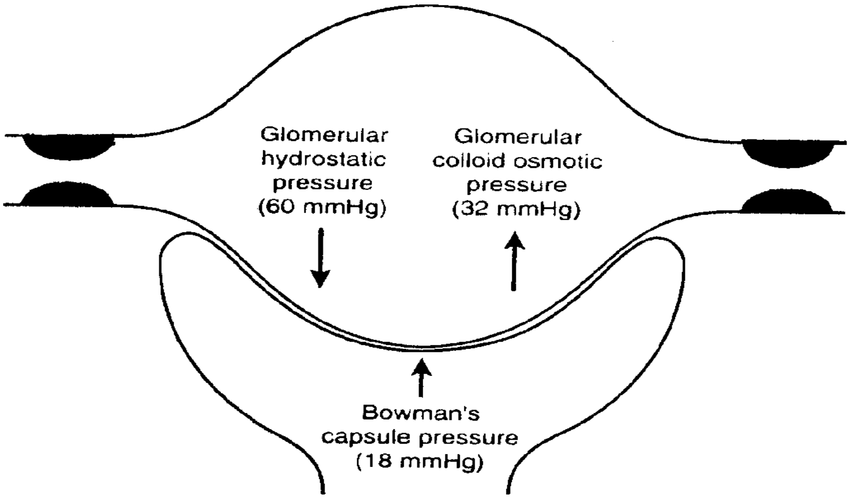
Forces opposing filtration (mmHg):

1) **HP_{BC}**= 18 mmHg. 2)**π** $_{GC}$ = 32 mmHg

.These values are estimates for the normal humans.

(Fig. 2-6) summarizes the forces causing filtration and those opposing by the glomerular capillaries. The net filtering pressure = 60 - 18 – 32

= 10 mmHg



K_F depends on:

1. Permeability of the glomerular membrane.
2. Surface area of the glomerular membrane.

K_F can not be measured directly, but it is estimated by dividing GFR by the net filtration pressure since:

GFR = **K_F** x net filtration pressure.

K_F = GFR / net filtration pressure = 125 ml / min /10 mmHg

= 12.5 ml / min /1 mmHg

K_F is the glomerular filtration rate per one mmHg of filtration pressure.

Factors that affect GFR:

From Starling equation, variations in the factors involved have predectable effect on GFR.

$GFR = K_F \times (HP_{GC} - HP_{BC}) - (\pi_{GC} - \pi_{BC})$

1- Changes in ultrafiltration coefficient (K_f):

K_f: An increased Kf raises the GFR where a decrease in Kf reduces the GFR.

K_f is affected by:

1) Surface area of the glomerular capillaries:

It's affected by:

a) Contraction of mesangial cells will reduce the surface area available for filtration; as contraction at points where the capillary loops bifurcate shifts the blood flow from some capillary loops.

The following agents cause contraction of the mesangial cells and therefore ***decrease GFR***

- Vasopressin
- Norepinephrine
- ThromboxaneA2
- Histamine
- Leucotrines A and D
- Endothelins
- PGF2

b) Agents causing relaxation of mesangial cells with consequent ***increase of GFR.***

- cAMP
- PGE2
- ANP
- Dopamine

c) Some diseases lower K_F by reducing the number of the functional glomerular capillaries, with reduction of surface area for filtration e.g. chronic uncontrolled diabetes mellitus.

2) Permeability: Increasing the thickness of the glomerular capillary membrane will reduce its permeability e.g. in chronic uncontrolled diabetes mellitus and hypertension.

II. Changes in the glomerular capillary hydrostatic pressure:

Increases in glomerular hydrostatic pressure raise GFR, whereas decreases in HP_{GC} reduce GFR:

Glomerular hydrostatic pressure is determined by:

1. Diameter of the afferent arteriole:

a) Vasodilatation of the afferent arteriole ➔ *++* HP_{GC} ➔++ GFR

e.g. bradykinins, PGE_2 and PGI_2 .

b) Vaso-constriction of the afferent arteriole e.g. by noradrenaline during sympathetic stimulation➔ decrease HP_{GC}➔ decrease GFR..

The increased sympathetic activity that occurs during exercise may reduce GFR to less than 50% of normal.

2. Diameter of the efferent arteriole:

Moderate vasoconstriction of the efferent arteriole➔ increases the resistance to the outflow from the glomerular capillaries. This raises the HP_{GC}➔slight increase of GFR. e.g. angiotensin II.

3. Arterial blood pressure:

The renal blood flow and GFR are kept relatively constant despite marked changes in arterial blood pressure (between 90-220 mmHg) by autoregulatory mechanisms.

Increased arterial pressure tends to raise HP_{GC} and to increase GFR. However, this effect is buffered by autoregulatory mechanisms. However, when the mean systemic pressure drops below 75 mmHg, there is a sharp drop in GFR.

Mechanisms of autoregulation:

a) Myogenic autoregulation:

Discussed before in regulation of renal blood flow.

This response is rapid and it is the first line of defense against rapid change in blood pressure. An increase in ABP results in stretching of the afferent arteriolar wall ➔ contraction of the smooth muscles and returns the diameter towards normal to minimize change in glomerular capillary pressure. Conversely a decrease in ABP results in relaxation of smooth muscle.

b) Tubulo-glomerular feed back:

Is responsible for autoregulation of renal blood flow**.**Discussed before in regulation of renal blood flow

III. Changes in Bowman's Capsule Hydrostatic Pressure:

- Increasing HP_{BC} reduces GFR.
- A stone in the ureter that obstructs the outflow of urine from the ureter will decrease GFR by raising HP_{BC}.

IV. Changes in the glomerular colloid osmotic pressure:

- Changes in the concentration of plasma proteins affect GFR as follows:

1. An increase in π_{GC} e.g. in dehydration will decrease GFR.
2. A decrease in π_{GC} e.g. in cases of hypoproteinemia will increase GFR.

V. Renal Vasodilators:

- PGE_2, PGI_2 and bradykinin produce renal vaso-dilatation, and increase in renal blood flow and GFR.
- Administration of anti-inflammatory drug like aspirin that block PG synthesis may cause marked reduction in GFR.
- Prostaglandin synthesis in the kidneys in increased by sympathetic nervous system stimulation and angiotensin II. This may protect the renal vessels from severe vasoconstriction during high sympathetic activity and elevated angiotensin II in situation of severe cardiovascular stress like haemorrhage.

VI. Autonomic nerves:

Sympathetic stimulation produces vasoconstriction of renal vessels with decrease in renal blood flow and glomerular filtration rate (mediated by α – adrenergic receptor). This occurs during exercise and rising from the supine to the standing position and when the systemic blood pressure falls

VII. Effect of protein intake:

- High protein intake increases renal blood flow and GFR.
- ***Mechanism:***

High protein intake ➔rise of amino acids into the blood➔filter in Bowman's capsule.

Increased amino acids reabsorption stimulate sodium reabsorption in the proximal tubules. This decreases sodium delivery to the macula densa which in turn elicits tubuloglomerular feedback afferent arteriole vasodilatation and efferent arteriole vasoconstriction that raises HPoc and GFR.

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